

## INTERNATIONAL SEARCH REPORT

Application No

PCT/NL 03/00804

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 7 A61K47/48

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, PAJ, WPI Data, CANCERLIT, CHEM ABS Data, BEILSTEIN Data, BIOSIS, EMBASE, DISSERTATION ABS

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 965 566 A (GREENWALD RICHARD B ET AL) 12 October 1999 (1999-10-12) figures 5,8-10; examples 20,29-31	1-42, 44-55
X	WO 98/19705 A (SQUIBB BRISTOL MYERS CO) 14 May 1998 (1998-05-14) examples 20,21,28-31,33,34	1-42, 44-55
X	EP 0 648 503 A (BEHRINGWERKE AG ; HOECHST SA LAB (FR)) 19 April 1995 (1995-04-19) examples claims	1-42, 44-55
X	WO 98/13059 A (SQUIBB BRISTOL MYERS CO) 2 April 1998 (1998-04-02) examples 2,7	1-42, 44-55
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Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

## \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*8\* document member of the same patent family

Date of the actual completion of the international search

10 March 2004

Date of mailing of the international search report

18/03/2004

Name and mailing address of the ISA

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 1 243 276 A (BEUSKER PATRICK HENRY ; SCHEEREN JOHANNES WILHELM (NL); VOS DICK (NL);) 25 September 2002 (2002-09-25) examples claims	1-55
Y	EP 0 693 485 A (TANABE SEIYAKU CO) 24 January 1996 (1996-01-24) examples claims	1-55
Y	EP 0 647 450 A (BEHRINGWERKE AG) 12 April 1995 (1995-04-12) examples claims	1-55
Y	EP 0 642 799 A (BEHRINGWERKE AG ; HOECHST SA LAB (FR)) 15 March 1995 (1995-03-15) examples claims	1-55
Y	DUBOWCHIK G M ET AL: "Cathepsin B-sensitive dipeptide prodrugs. 2. models of anticancer drugs paclitaxel (Taxol(>R)), mitomycin C and doxorubicin" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 8, no. 23, 1 December 1998 (1998-12-01), pages 3347-3352, XP004143756 ISSN: 0960-894X table 1 figure 1 schemes	1-55
Y	DE GROOT FRANCISCUS M H ET AL: "Synthesis and Biological Evaluation of Novel Prodrugs of Anthracyclines for Selective Activation by the Tumor-Associated Protease Plasmin" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, US, vol. 42, no. 25, 1999, pages 5277-5283, XP002168683 ISSN: 0022-2623 abstract schemes	1-55

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DUBOWCHIK G M ET AL: "Cathepsin B-sensitive dipeptide prodrugs. 1. A model study of structural requirements for efficient release of doxorubicin" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 8, no. 23, 1 December 1998 (1998-12-01), pages 3341-3346, XP004143755 ISSN: 0960-894X scheme 1 table 1 figure 2	1-55
Y	EP 0 665 020 A (SQUIBB BRISTOL MYERS CO) 2 August 1995 (1995-08-02) examples claims	1-55
Y	WO 00/34231 A (JONES DAVID S ; JOLLA PHARMA (US)) 15 June 2000 (2000-06-15) examples figures claims	1-55
Y	KAR A K A K ET AL: "Synthesis and evaluation of daunorubicin-paclitaxel dimers" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 10, no. 3, February 2000 (2000-02), pages 261-264, XP004188830 ISSN: 0960-894X page 262	1-55
Y	APPENDINO G ET AL: "Synthesis of Paclitaxel (Docetaxel)/2-Deacetoxytaxinine J Dimers" TETRAHEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 55, no. 21, 21 May 1999 (1999-05-21), pages 6567-6576, XP004165623 ISSN: 0040-4020 structures schemes	1-55
Y	WO 02/26220 A (UNIV NORTH CAROLINA) 4 April 2002 (2002-04-04) examples claims figures	1-55
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Application No  
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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>GROOT DE F M H ET AL: "IN VIVO EFFICACY OF SPACER-CONTAINING ANTITUMOR PRODRUGS OF DOXORUBICIN DESIGNED FOR SPECIFIC ACTIVATION BY TUMOR-ASSOCIATED PLASMIN" PROCEEDINGS OF THE ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, NEW YORK, NY, US, vol. 43, March 2002 (2002-03), page 415, XP008007701 ISSN: 0197-016X the whole document &amp; 93rd Annual Meeting of the American Association for Cancer Research; San Francisco, California, USA; April 06-10, 2002 abstract</p>	1-55
Y	<p>GROOT DE FRANCISCUS M H ET AL: "Elongated Multiple Electronic Cascade and Cyclization Spacer Systems in Activatable Anticancer Prodrugs for Enhanced Drug Release" JOURNAL OF ORGANIC CHEMISTRY, AMERICAN CHEMICAL SOCIETY. EASTON, US, vol. 66, 2001, pages 8815-8830, XP002212035 ISSN: 0022-3263 abstract figures</p>	1-55
Y	<p>GROOT DE F M H ET AL: "Synthesis and Biological Evaluation of 2'-Carbamate-Linked and 2'-Carbonate-Linked Prodrugs of Paclitaxel: Selective Activation by the Tumor-Associated Protease Plasmin" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 43, 2000, pages 3093-3102, XP002212034 ISSN: 0022-2623 abstract</p>	1-55
Y	<p>GROOT DE F M H ET AL: "DESIGN, SYNTHESIS AND INITIAL BIOLOGICAL EVALUATION OF AN ALPHA V<math>\beta</math>3-INTEGRIN-TARGETED PLASMIN SENSITIVE DOXORUBICIN PRODRUG" PROCEEDINGS OF THE ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, NEW YORK, NY, US, vol. 43, March 2002 (2002-03), page 144, AN2059, XP001051142 ISSN: 0197-016X the whole document</p>	1-55

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International application No.  
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## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claims 45-49 are directed to a diagnostic method practised on the human/animal body, and claim 55 to a method of treatment of the human/animal body, a search has been carried out, based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 1-42, 44-55 in part  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

## Continuation of Box I.1

Although claims 45-49 are directed to a diagnostic method practised on the human/animal body, and claim 55 to a method of treatment of the human/animal body, a search has been carried out, based on the alleged effects of the compound/composition.

## Continuation of Box I.2

Claims Nos.: 1-42, 44-55 in part

Present claims 1-42, 44-55 relate to an extremely large number of possible compounds, compositions containing them, as well as to their use. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds prepared on the examples, and to the compounds specifically mentioned in claim 43.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

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